REMARKS

Claims 1-9, 11, 13-18, 20-21, and 30-31 are currently pending in this application. Claims 1, 31, and 32 have been amended to reference that it is a method of screening a library of polynucleotide sequences for a polynucleotide sequence having or encoding a "desired activity or function" instead of a "desired characteristic," though the terms are interchangeable. Support for the amendments is found throughout the specification, including at page 6, line 4 to line 8 and page 6, line 22 to 32 (which generally describes what an activity or function of interest is), and page 8, lines 18 to page 9, line 9 (which lists numerous activities or functions of interest).

In addition, claim 1 now also incorporates the amendments which were mistakenly omitted from the Clean Version of the claims presented in the previously submitted amendment, but shown in the Version with Markings to Show Changes Made.

It is respectfully submitted that the present amendment presents no new issues or new matter and places this case in condition for allowance. Reconsideration of the application in view of the above amendments and the following remarks is requested.

I. The Rejection of Claims 1-9, 11, 13-18, 20-21, 30-32 under 35 U.S.C. 103

Claims 1-9, 11, 13-18, 20-21, and 30-32 are rejected under 35 U.S.C. 103 as being unpatentable over Christensen (WO 98/01470) in view of Aleksenko et al (Mol. Microbiol. (1996) 19(3), 565-574) and Dalboge et al (Mol. Gen. Genet (1994) 243-260). The Office contends that Christensen teaches that a transcription factor regulating alpha-amylase promoter initiated expression in filamentous fungi, DNA sequences encoding for this factor, and transformation into and expression in fungal hosts. The Office states that Aleksenko teaches the AMA 1 plasmid vector and that it has enhanced co-transformation efficiency. The Office states that Dalboge teaches a fungal selection marker. The Examiner contends it would be obvious to use the AMA-1 of Aleksenko with the fungal selection marker in the vectors of Christensen.

Applicants responded to the rejection by pointing out that the references do not alone or in combination suggest the use of the AMA-1 related replication initiating sequences recited in the claims and a fungal selection marker for use in screening a library of polynucleotides sequences.

The Office has now responded by asserting that:

(1) a person skilled in the art would know how to make a library of vectors with each vector having variant sequences encoding different versions of a protein of interest;

(2) applicants are improperly attacking the references individually, whereas the rejection is based on the combined teachings;

(3) applicants arguments "are based on a single reference, and since the instant claimed method steps are incomplete and do not include any specific methods to identity th polynucleotides sequences of interest from the population of vectors; and it would be obvious to one skilled in the art at the time the invention was made to use the teachings of Christensen et al, Aleksenko et al. and Dalboge et al in the method of screening a library of polynucleotides of interest in fungal cells such that enhance expression of the polypeptide of interest is produced in host cells";

(4) although Applicants recite that there is a difference between screening a gene library from screening a variant library, that the features upon which Applicants relies are not cited in the claims; and

(5) Applicants arguments regarding screening would not read on instant claim 31 because it is drawn to a method of constructing a library of polynucleotide sequences of interest and Applicants are requested to include specific method steps in the method of screening a variant library for a polynucleotide sequence of interest.

This rejection is respectfully traversed. Foremost, Applicants note that a misunderstanding is apparent form the Offices' statement that: "Applicants assert that the Aleksenko et al is co-authored by the inventors..." (emphasis added). Applicants are not the co-authors of the Aleksenko et al reference, and Applicants statements were not intended to make such an assertion. Rather, Applicants simply intended to make reference to another publication authored by Aleksenko et al. (Fungal Genetics and Biology (1997) 21:373-387).

With respect to the obviousness rejection, the Office is apparently focusing on the screening assay as a critical point for how the claims differ from the prior art. In particular, the Office focuses on the nature of the recited screening-assay as an essential feature of the present invention, while only making a passing reference to the invention being a method of screening a library for a polynucleotide of interest. The particular nature of the assay used to screen for an activity or function of interest encoded by the members of the polynucleotide library, however, is not the key point of distinction over the cited art. Rather, a key point of distinction from the cited art is that the present invention provides a method for screening a library of nucleic acids encoding different versions of polynucleotides in filamentous fungal cells by providing a transformation process which makes it possible to obtain uniform expression of a variant polynucleotide library in filamentous fungal cells, without performing cumbersome chromosomal integration. Applicants have provided a new method for screening a library polynucleotides which uses a fungal selection marker polynucleotide sequence and a sp cific

fungal replication initiating polynucleotide sequence, wherein the marker and the replication initiating sequence do not vary within the population; and wherein the replication initiating sequence is a nucleic acid sequence selected from the group consisting of: (1) a replication initiating sequence having at least 80% identity with the nucleic acid sequence of SEQ ID NO:1 or SEQ ID NO:2, as determined using the GAP computer program with a GAP creation penalty of 5.0 and GAP extension penalty of 0.3, and is capable of initiating replication; and (2) replication initiating sequence which hybridises under low stringency conditions with (i) the nucleic acid sequence of SEQ ID NO:1 or SEQ ID NO:2, or (ii) the respective complementary strands, wherein the low stringency conditions are defined by prehybridization and hybridization at 42°C in 5x SSPE, 0.3% SDS, 200 mg/ml sheared and denatured salmon sperm DNA, and 25% formamide, and wash conditions are defined at 50°C for 30 minutes in 2x SSC, 0.2% SDS.

None of the cited reference, alone or in combination, teach or suggest the use the recited fungal selection marker polynucleotide sequence and a fungal replication initiating polynucleotide sequence in a vector for screening a library of polynucleotides having different versions of polynucleotide sequences of interest.

Christensen discloses a transcription factor derived from a strain of the filamentous fungus *Aspergillus oryzae*. The gene encoding the transcription factor, denoted *amyR*, was isolated in a complementation experiment, the outline of which in a simplified manner follows (page 18, Example 1): An *A.oryzae* mutant-strain ToC 879 was constructed, wherein a lipase gene was placed under the transcriptional control of the TAKA-amylase promoter; the mutant did not exhibit lipase activity. Since the TAKA-promoter requires a transcription factor to be active, any lipase activity in the mutant would be a positive indication of the presence of the transcription factor in the mutant. The gene encoding the transcription factor was isolated by co-transforming the mutant with an *A. oryzae* cosmid library, *i.e.*, a whole genome library, and an autonomously replicating pHelp1 based plasmid, and then screening the co-transformants for lipase-positive clones. The pHelp1 based plasmid of Christensen comprises the AMA1 autonomously replicating sequence (Clutterbuck (1991) Gene 98, 61-67).

Aleksenko et al discloses a detailed study of the AMA1 autonomously replicating sequence isolated from *Aspergillus nidulans*, including its nucleotide sequence.

Accordingly, Christensen and Aleksenko are not directed to, and do not suggest, screening a variant polynucleotide library, that is, a library having different versions of polynucleotides sequences of interest. Rather, both Christensen and Aleksenko are directed to gene expression studies, i.e., to methods for screening a genomic library. A genomic library is

very different from a variant polynucleotide library, that is, a library having diff rent versions of polynucleotides sequences of interest. In this regard, the only motivation provided by Christensen and Aleksenko is to use AMA-1 in a gene expression study; there is no motivation to use AMA-1 in vectors carrying different versions of polynucleotides sequences of interest for screening such a variant library.

Dalboge et al. do not cure the deficiencies of Christensen and Aleksenko. Dalboge et al disclose methods for isolating genes from cDNA gene-libraries derived from filamentous fungal cells, by expression cloning in yeast host cells. There is no suggestion in Dalboge et al. that an AMA-1 sequence would be suitable for use in screening a variant library in a fungal cell.

Finally, with respect to the specific allegations (shown below in italics) made by the Office action, Applicants respond as follows:

(1) a person skilled in the art would know how to make a library of vectors with each vector having variant sequences encoding different versions of a protein of interest.

Applicants acknowledge that an artisan would know how to make a library of vectors encoding different versions of a protein of interest, however, as discussed, the cited art does not suggest the use of the vectors recited in process step (a) for screening a library that encodes different versions of the polynucleotide sequence of interest.

(2) applicants are improperly attacking the references individually, whereas the rejection is based on the combined teachings.

As discussed above, the combination of references does not suggest the claimed invention as there is no motivation in any of the cited references that the vectors recited in process step (a) would be useful for screening a library polynucleotide sequence that encode different versions of the polynucleotide sequence of interest, which is very different form the genomic libraries of Christensen and Aleksenko.

(3) applicants arguments "are based on a single reference, and since the instant claimed method steps are incomplete and do not include any specific methods to identity the polynucleotides sequences of interest from the population of vectors; and it would be obvious to one skilled in the art at the time the invention was made to use the teachings of Christensen et al, Aleksenko et al. and Dalboge et al in the method of screening a library of polynucleotides of interest in fungal cells such that enhance expression of the polypeptide of interest is produced in host cells".

Again, as previously discussed, th cit d references do not suggest that the vectors recited in process step (a) would be useful for screening a library polynucleotide sequence that encode different versions of the polynucleotide sequence of interest.

(4) although Applicants recite that there is a difference between screening a gene library from screening a variant library, that the features upon which Applicants relies are not cited in the claims.

Applicants respectfully point out that the difference between screening a gene library and a variant library are clearly features of the claimed invention, as process step (a) (ii) clearly recites that the vectors in the population that vary from other vectors in the population by carrying different versions of the polynucleotide sequence of interest. Such recitation clearly distinguishes the claims from the gene expression studies of Christensen and Aleksenko.

(5) Applicants arguments regarding screening would not read on instant claim 31 because it is drawn to a method of constructing a library of polynucleotide sequences of interest and Applicants are requested to include specific method steps in the method of screening a variant library for a polynucleotide sequence of interest.

As previously discussed, the key aspect of the invention is not the particular assay used to identify (screen for) the polynucleotide sequence of interest. Indeed, the skilled artisan can use any method (assay) suitable to identify an activity or function associated with the polynucleotides of interest.

For the foregoing reasons, Applicants submit that the claims overcome this rejection under 35 U.S.C. 103. Applicants respectfully request reconsideration and withdrawal of the rejection.

II. The Rejection of Claims 1-9, 11, 13-18, 20-21, 30-32 under 35 U.S.C. 112

Claims 1-9, 11, 13-18, 20-21, 30-32 are rejected under 35 U.S.C. 112 as being indefinite for failing to particularly point out and distinctly claim the subject matter which Applicant's regards as the invention. The Examiner has maintained this objection for reason of record, that is, because "the claims do not recite how the transformants are selected". This rejection is respectfully traversed.

As is clear from the above discussion, the instant invention relates to "a method for screening a library of polynucleotide sequences of interest having or encoding a desired activity or function in filamentous fungal cells".

How the transformants are selected depends on *what the desired activity or function is in each embodiment of the invention.* Any appropriate selection procedure is clearly applicabl

and is covered by the claims. For example, if the desired activity is improved thermostability of an enzyme, then, e.g., an activity-based assay at high temperature can be employed.

Plainly, it is improper and an undue restriction to limit the claims to a single or preferred selection method, when the invention contemplates and is broadly applicable to the use of any appropriate selection method, and when such selection methods are clearly well-within the skill of an artisan practicing the claimed invention.

Thus, the claims are not indefinite for lacking an essential step as the phrase "selecting or screening for one or more transformants expressing the desired activity or function" is not so narrow as to encompass only a particular assay, and an artisan would clearly understand that this phrase encompasses the many procedures well-known in the art for identifying one or more transformants expressing a desired activity.

For the foregoing reasons, Applicants submit that the claims overcome this rejection under 35 U.S.C. 112. Applicants respectfully request reconsideration and withdrawal of the rejection.

III. Conclusion

In view of the above, it is respectfully submitted that all claims are in condition for allowance. Early action to that end is respectfully requested. The Examiner is hereby invited to contact the undersigned by telephone if there are any questions concerning this amendment or application.

Respectfully submitted,

Date: November 11, 2003

Jason I. Garbell, Reg. No. 44,116
Novozymes North America, Inc.
500 Fifth Avenue, Suite 1600
New York, NY 10110
(212) 840-0097